



# IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

**Review Article**

September 2020 Vol.:19, Issue:2

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## Novel Trend in Medical Field – Niosome - A Review



**IJPPR**  
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals



ISSN 2349-7203

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**Submission:** 20 August 2020  
**Accepted:** 26 August 2020  
**Published:** 30 September 2020

**Keywords:** Niosomes, Surfactants, factors, Applications

### ABSTRACT

In recent years, niosomes as a drug carrier has been received much attention in pharmaceutical industry research and academic research. Niosomes and liposomes are similar in drug delivery potential both increase the drug efficacy as compared thereupon of free drug. Non-ionic surfactant vesicles are preferred over liposomes because it exhibits high chemical stability, economy, easy handling, and storage. Non-ionic surfactant vesicles are microscopic lamellar structures. Niosomes are formed on the admixture of the different classes of surfactants and cholesterol with subsequent hydration in aqueous media. This review represents the structure of niosome, advantages, disadvantages, methods of preparation, and applications.



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## INTRODUCTION

Niosomes are the kind of non-ionic surfactant unilamellar or multilamellar vesicles it counting on the strategy won't to prepare them <sup>[1]</sup>. Which are non-toxic, biodegradable, more stable, biocompatible, inexpensive, non-immunogenic, long time periods, and achieves the delivery of drugs at the target site in an exceedingly sustained and/or controlled manner. It's another for liposomes. The niosomes are very small and microscopic in size and also their size lies within the nanometric scale and the size ranges between 10 to 1000nm. Non-ionic surfactants like span (20, 40, 60, and 80) and cholesterol as a stabilized additive are the most common components of those micro/nanocarriers. For the formulation of niosomes mainly used surfactants are span (20,40,60,80), tween (20,60,72,76,78), poloxamers, Brij etc. The niosomal carrier (surfactant/cholesterol) can significantly increase the entrapment efficiency of the drugs. The drug entrapment efficiency increases because of the interaction between the drugs and therefore the acyl chains of span 60 <sup>[2]</sup>. Additionally, some ionic amphiphiles like dicetyl phosphate (DCP), stearyl amine (SA), phosphatidic acid (negatively charged molecules) and cetyl pyridinium chloride (positively charged molecule) are utilized in the niosome formulations for the loading of medication, enhancing stability and increasing efficacy, etc. <sup>[3]</sup>. Charged molecules of the niosome can even increase the steadiness of formulation thanks to an appropriate zeta potential. The particles with a high zeta potential are show less tendency to aggregate thanks to electrical repulsion <sup>[4, 5]</sup>. The vesicular structure of the niosome was maintained because of the Van der Waals forces among surfactant molecules, entropic repulsive forces of the pinnacle groups of surfactants, repulsive forces emerging from the electrostatic interaction between charged groups of surfactant molecules, short-acting repulsive forces, etc. These forces are to blame for maintaining the structure of niosomes. These may act as a depot, releasing the drug during a controlled manner restricting effects to focus on cells. The niosomal vesicles have the capability to carry both hydrophilic and lipophilic drugs. And that they have the flexibility to focus on vaccines and medicines to the reticuloendothelial system. The reticuloendothelial system (RES) preferentially takes up the non-ionic surfactant vesicles. The uptake of niosomes is controlled by the opsonins, which mark the niosomes for clearance while delivering the cargo to the antigen-presenting cells <sup>[6]</sup>. The niosomes can even be utilized for targeting drugs to organs apart from the reticuloendothelial system. A carrier system (such as anti-bodies) may be attached to niosomes (as immune globulins) which binds readily to the lipid surface of the niosome) to focus on them to specific organs <sup>[7]</sup>.

Niosomes are mainly formulated in oral, parenteral, topical, ocular dosage forms, etc. Oral niosomal formulations show greater bioavailability of poorly absorbed drugs and reduce GI irritation. It helps to attenuate drug toxicity because of slow release and requires a touch of medication. Topical niosomal formulation shows better penetration of medication through the skin, providing a sustained pattern of drug release, increasing the stability of the drug, and have the capability to hold both hydrophilic and lipophilic drugs. Niosomal carriers are suitable for the transdermal delivery of diverse pharmacological agents like anti-cancer, anti-microbial, antioxidant, anti-inflammatory, and anti-bacterial molecules. Ophthalmic niosome have the flexibility to deliver the therapeutic agent to a patient in a staggered profile. The key drawbacks of the standard drug delivery systems are lacking of permeability through the ocular barrier and poor bioavailability of water soluble drugs etc. These varieties of drawbacks are overcome by the emergence of niosomes. The drug loaded niosomes will be fabricated by easy techniques with improved physical stability and it also enhances the bioavailability without blurring the vision.

Other advantages are,

- To control the discharge of drug
- To target drugs at the situation



Intravenous niosomal preparations are going to be prevent incompatibilities between two drugs. Eg: Acyclovir and Vancomycin that are commonly used for the treatment of acute meningitis. Other advantages are:

- Sustained release of drugs
- Protect the drug from degradation
- Reduce the frequency of administration etc.

## CONSTITUTION OF A NIOSOME VESICLE

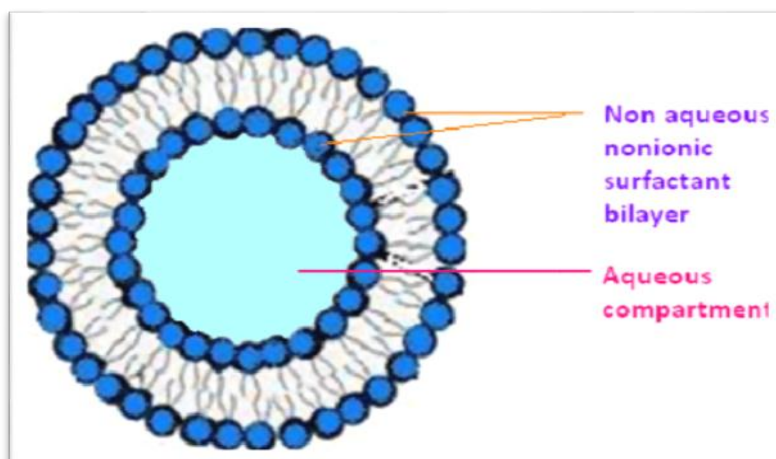


Figure No. 1: Structure of non-ionic surfactant vesicle.

### Constitution

It mainly has two components.

### Cholesterol

This is used to provide rigidity and proper shape to niosomes. It is a steroid derivative. The proper amount of cholesterol is added to the niosomes to get the most stable formulation due to its interaction with non-ionic surfactant<sup>[8]</sup>.

### Non-ionic surfactants

They have the hydrophilic head group and hydrophobic tail group. The hydrophilic group effects on entrapment efficiency of drugs. The size of the niosome depends upon the HLB value of the surfactant. If the HLB value increases alkyl chain increases, so the size of niosome increases<sup>[9]</sup>. The HLB values 8.6 have the highest entrapment efficiency<sup>[10]</sup>. The different types of non-ionic surfactants are fatty alcohol, ethers, esters, and block polymers.

### Other additives

They are charge inducers. Both positively and negatively charged molecules are used to induce a charge in niosomal formulations. Which prevents vesicles aggregation, fusion, and flocculation, and increases the surface charge density and they stabilize the formulation<sup>[11]</sup>.

Eg: dicetyl phosphate (DCP), stearyl amine (SA)

## ADVANTAGES

- Their surface formation and modification is extremely easy because of the functional groups on their hydrophilic heads.
- Have high compatibility with the biological system.
- They can improve the therapeutic performance of the drug by protecting it from the biological environment, leading to better availability and controlled drug delivery.
- They improve the therapeutic profile of drug molecules due to delayed clearance for the circulation <sup>[12, 13]</sup>.
- They can improve the permeation of drugs through the skin. The niosomal bilayers protect the therapeutic drug molecules from the various factors present within the body.
- Provide the advantage of usage through various routes like oral, parenteral, topical and ocular, etc.
- The structure of the non-ionic surfactant vesicles can accommodate hydrophilic, hydrophobic, and amphiphilic drug moieties.
- The vesicles can act as a depot to release the active pharmaceutical ingredient in a controlled manner.
- They are osmotically active and stable.
- The water-based vesicle suspension offers greater patient compliance compared to oil-based systems.
- Access to raw material is convenient.
- Low toxicity because of the non-ionic nature of surfactants.
- Targeted drug delivery is often achieved using niosomes the drug delivered on to the piece where the therapeutic effect is required.
- They improve the oral bioavailability of poorly soluble drugs.
- A reduced dose is required to know the required effect.
- They increase the stability of the entrapped drug.

- They are biodegradable, non-immunogenic, and biocompatible.
- Drug protection from enzyme metabolism.

### DISADVANTAGES

- Hydrolysis of encapsulated drugs which limit the quantity of the dispersion.
- May require specialized equipment.
- An increase in the polyoxyethylene chain length enhances cytotoxicity.
- Inefficient drug loading.
- Physical and chemical instability.
- Time consuming.
- Fusion.
- Leaking of the entrapped drug.
- Aggregation.

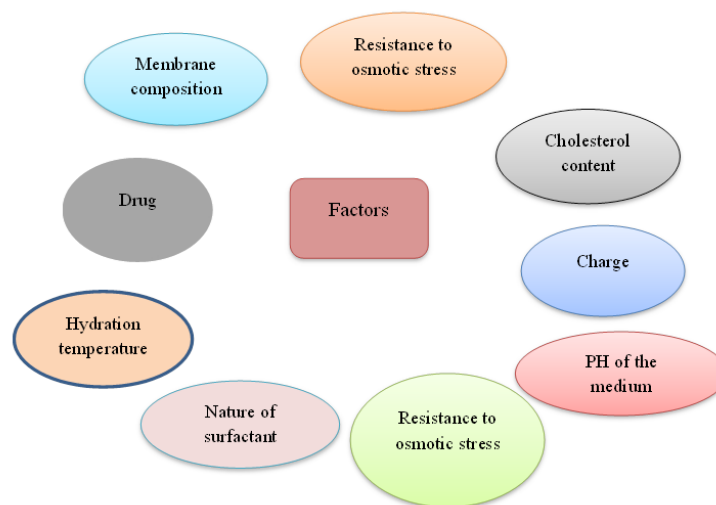


### TYPES OF NIOSOMES

They mainly two type

According to the nature of lamellarity	According to the size
Multilamellar vesicles(MLV) : 1-5 $\mu$ m in size	Small niosome (100nm – 200nm)
Small unilamellar (SUV): 25- 500 nm in size	Large niosome (800nm – 400nm)
Large unilamellar vesicles (LUV) : 0.1- 1 $\mu$ m in size	Big niosomes (2 $\mu$ m -4 $\mu$ m)

## FACTORS AFFECTING FORMATION OF NIOSOMES



**Figure No. 2: Various factors affecting the formation of niosomes**

**1. Nature of Surfactant:** Surfactant HLB value also affects the mean size of the niosomes. The HLB value increases the mean size of niosomes and surfactant hydrophobicity increases with the decrease in surface free energy<sup>[14]</sup>. The quantity of surfactant decreases the niosomal drug release is increases because of the permeability of the encapsulated drug is decreasing.

**2. Nature of Encapsulated Drug:** The non-ionic surfactant vesicles bilayer's rigidity and charge influences the physiochemical property of the drug molecules. The HLB of drug influences the degree of drug entrapment<sup>[15]</sup>.

**3. Hydration Temperature:** The size and shape of the niosome are affected by the hydration temperature. Improper selection of the hydration temperature, time, and hydration medium volume produces fragile niosomes or drug leakage problems may arise<sup>[16]</sup>. These factors are considered as critical factors.

**4. Cholesterol Content:** The use of cholesterol leads to an increase in the rigidity of the niosomal bilayers, increases the entrapment efficiency and hydrodynamic diameter of niosomes. An increase in cholesterol concentration causes a decrease in the release rate of encapsulated material<sup>[17]</sup>.

**5. Charge:** Presences of positive or negative charge leads to an increase in interlamellar distance between successive bilayers in multilamellar non-ionic surfactant vesicle structure and greater overall entrapped volume.

**6. Resistance to Osmotic Stress:** The addition of hypertonic solution causes a reduction in vesicle diameter. In a hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by the faster release due to the mechanical loosening of vesicle structure under osmotic stress.

## PREPARATION OF NIOSOMES

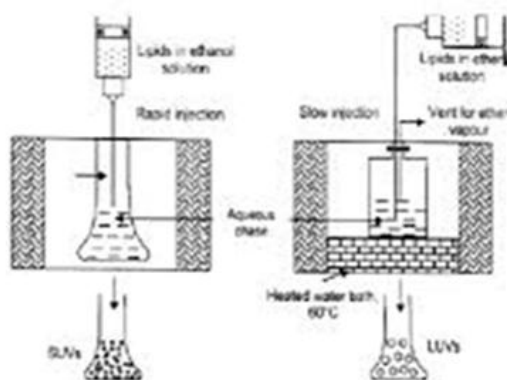
Three basic general steps are used to prepare the niosomes.

1. Hydration of mixture of the surfactants at elevated temperature,
2. Sizing of prepared niosomes,
3. Removal of untrapped materials from the niosomal vesicles by using different methods.

### Different methods for the preparation of niosomes

#### 1) Ether injection method

In this method, a suitable amount of the surfactants dissolved in diethyl ether. Then it slowly injected through 14 gauge needle in to warm water maintained at 60<sup>0</sup>c.vaporization of organic phase leads to the formation of single-layered niosome vesicles. The diameter of the vesicle range from 50 to 1000 nm<sup>[18, 19]</sup>. It also depends upon the condition used for the preparation of vesicles.



**Figure No. 3: Ether injection method**



## 2) Ethanol injection method

In this method surfactant dissolved in ethanol and this mixture injected rapidly through a fine needle into an excess of saline or another aqueous medium. The vaporization of ethanol leads to the formation of niosomal vesicles<sup>[20]</sup>.

## 3) Sonication

It is a conventional method. Bath and probe sonications are used for niosome preparation. This method can decrease the diameter of niosome with narrow size distribution<sup>[17]</sup>. Probe sonication uses high levels of energy and it may cause shedding of titanium and sudden increase of temperature these are the main drawback of probe sonication.

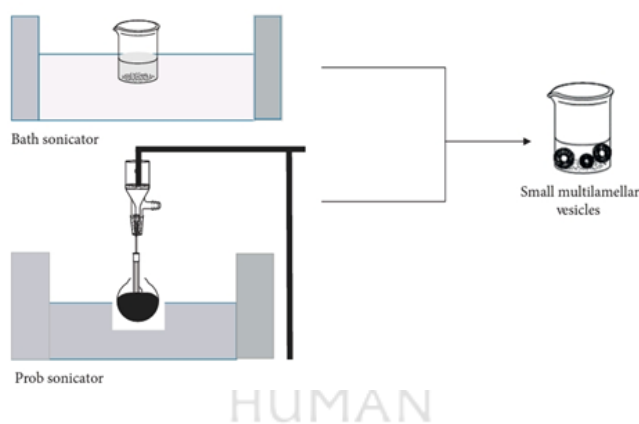


Figure No. 4: Sonication method

## 4) Reversed phase evaporation

Dissolving the non-ionic surfactants and other additives in an organic solvent (a mixture of ether and chloroform). An aqueous phase containing the drug is added to this and the resulting mixture is sonicated at 4-5<sup>0</sup>c. The organic phase is removed at 40<sup>0</sup>c under low pressure using a rotary evaporator. The resulting suspension is diluted with PBS to yield niosomes<sup>[21, 22]</sup>.

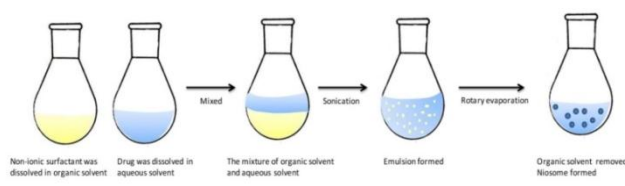


Figure No. 5: Reversed phase evaporation method

### 5) Formation of niosomes from proniosomes

It is a dry formulation of niosome. In this method, niosome is coated with non-ionic surfactants and water soluble carrier such as sorbitol this preparation is termed as proniosomes. These are easily hydrated into niosomes before usage. The advantages of this type of preparation are good physical and chemical stability, ease of scale-up, long term storage, and convenience for transportation [23, 24].

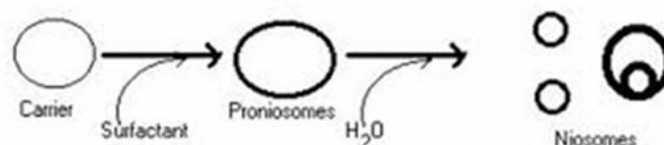


Figure No. 6: Formation of niosomes from proniosomes

### 6) Bubble method

It is one of the steps of the preparation of niosome and liposomes without using an organic solvent. The bubbling unit consists of three necks positioned round bottom flask. It helps to control the temperature. Nitrogen is supplied through one of the neck and other two necks positioned with a thermometer and water-cooled reflux. The surfactants and cholesterol is mixed together in PH 7.4 buffer at 70<sup>0</sup>c, for 15 seconds with a high shear homogenizer and immediately bubbled at 70<sup>0</sup>c by using the nitrogen gas [25].

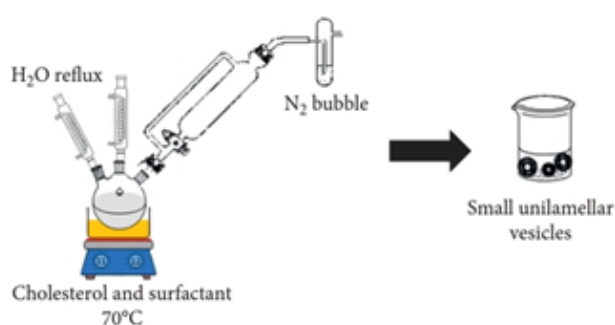
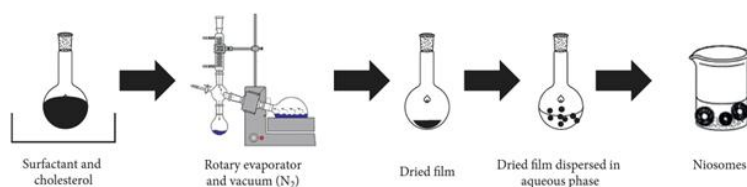


Figure No. 7: Bubble method

### 7) Thin film hydration technique

Rotary evaporator is one of the equipments used for in this method. Surfactant, cholesterol, and volatile organic solvents are mixed together in a round bottom flask. After the removal of the volatile solvent, the deposited thin layer of surfactant film can be rehydrated with an

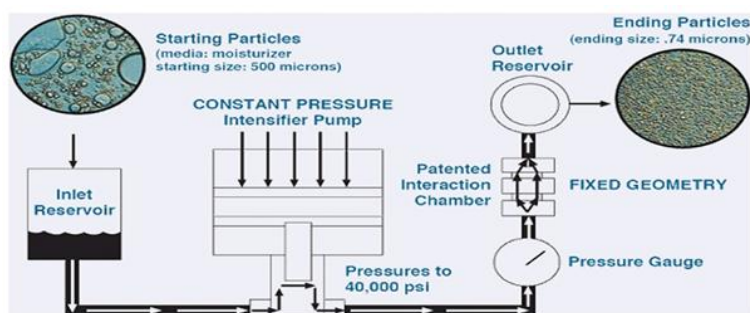
aqueous phase at 0-60<sup>0</sup>c with gentle agitation (the aqueous phase containing the drug). Finally, it is sonicated to acquire niosomes with narrow size distribution.



**Figure No. 8: Thin film hydration technique**

## 8) Microfluidization

This method is based on the submerged jet principle. Micro fluidizer is used as major equipment. In this method provides unilamellar, smaller size, greater uniformity, and better reproducibility of niosomes.



**Figure No. 9: Microfluidization**

## 9) Multiple membrane extrusion method

In this method surfactant, cholesterol, and dicetyl phosphate in chloroform are mixed together and the organic phase is evaporated. The dried thin film is hydrated with an aqueous drug solution. Then it extruded through polycarbonate membranes. It is the best method for controlling niosome's size [26].

## SEPARATION OF UNENTRAPPED DRUG

The various techniques are used for removing unentrapped drug from niosomes.

This includes:

1) **Dialysis:** The aqueous niosomal dispersion is dialyzed by using a dialysis tube for removing entrapped drug presenting in the niosomal dispersion. The phosphate buffer or normal saline or glucose solution is used as the dialyzing solution.

2) **Gel Filtration:** It is a chromatographic technique used for removing the untrapped drug from the niosomal dispersion. Sephadex g-50 is used as a column and the phosphate-buffered saline or normal saline is used as the eluent.

3) **Centrifugation:** The niosomal suspension is centrifuged and the supernatant is separated by using ultracentrifuge apparatus. The pellet is washed and then resuspended to obtain untrapped drug free niosomal suspension [27].

## APPLICATION

- **Niosomes in oral drug delivery**

An oral administration of niosomal formulation of different kind of poorly soluble drug exhibits higher drug absorption and low GI irritation. e.g.: niosomal formulation of methotrexate exhibits higher GI drug absorption compare to other same drug formulations [28].

- **Ophthalmic drug delivery**

Ocular dosage forms like an ophthalmic solution, suspension, ointment show drug impermeability of corneal epithelium, tear production, etc. But achieve good bioavailability of the drug by using vesicular systems like niosomes and liposomes.

Eg: niosomal drug formulation of timolol maleate

Increases bioavailability by 0.25% and decreases the cardiovascular side effects compared with other marketed formulations [29].

- **Pulmonary drug delivery**

An anti-asthmatic drug shows poor permeation through hydrophilic mucus in inhalation therapy. These problems are also overcome by the anti-asthmatic drug niosomal formulation.

Eg: Beclomethasone dipropionate niosomes show improved mucus permeation and therapeutic effect. It also shows sustained and targeted drug delivery [30].

- **Use in studying immune response and delivery of immunosuppressant drugs**

It is used to study the nature of the immune response provoked by antigens. Many niosomal formulations have been used for determining the nature of antigen produced immune response. Niosomes are potent adjuvant and also have low toxicity and greater stability.

Niosomes are a good platform for the delivery of immune suppressant drugs.

Immunosuppressants are mainly used for organ transplantation such as liver, heart, kidney, etc. Immunosuppressants possess serious side effects, and hence to be used carefully.

Eg: Mycophenolate mofetil niosomal suspension shows controlled delivery of drugs and reduces side effects<sup>[31]</sup>.

- **Gene delivery**

Niosomes have been widely used as oligonucleotide carriers for the treatment of many kinds of diseases.

Eg; Niosomes can also serve as a delivery system for targeting stem cells.

For DNA vaccines, niosomes can also be used as vectors, and provide a simple, stable, and cost-effective alternative compared with other method<sup>[32]</sup>.

- **Diagnostic imaging with niosomes**

Niosomal system can be used as diagnostic agents.

Eg: Niosomes are also considered as a carrier for diagnostic agent iobitridol for X-ray imaging. Niosomes are prepared by thin film method followed by sonication<sup>[33]</sup>.

- **Anti-hypertensive treatment**

Losartan potassium is an anti-hypertensive drug. The major problem with the therapy of this drug is poor bioavailability (32%), as a reason for its limited solubility, absorption, and first-pass metabolism.

Eg: The niosomal formulation of losartan potassium shows better oral bioavailability and to extends its release for a prolonged period<sup>[34]</sup>.

- **Cosmetics formulations**

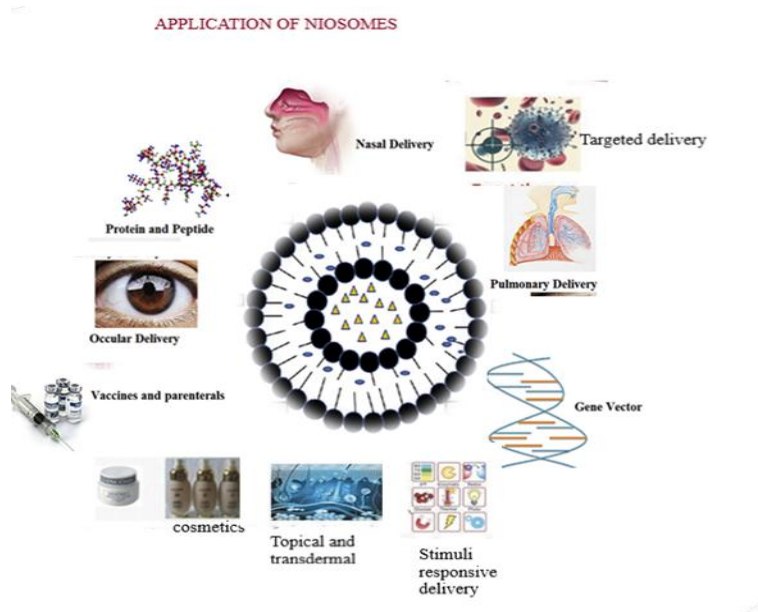
A Niosomal cosmetic formulation has ability to increase the stability of entrapped drugs and improve the bioavailability of poorly absorbed ingredients and enhances skin penetration [1].

Eg: the topical delivery of minoxidil in hair loss treatment.

- **Anti-neoplastic treatment**

Most antineoplastic drugs cause severe side effects and show poor bioavailability. Numerous attempts have been made to enhance the selectivity of anti-neoplastic agents by linking them to cancer moiety.

Eg: Cisplatin niosomes are protective against bone marrow toxicity and weight loss as compared to free cisplatin. The other anti-cancer drugs like doxorubicin, methotrexate, bleomycin, vincristine show better therapeutic activity and lesser side effects [35].



**Figure No. 10: Application of niosomes**

## CONCLUSION

Niosomes are novel drug carriers to design effective drug delivery systems. They provide an excellent opportunity for loading different types of drugs (hydrophilic, lipophilic, or both drugs together). Non-ionic surfactant vesicles or niosomes are one of the best carriers for transporting a drug molecule to its site of action. It is the best example of great evolution in Nanotechnology. It protects the drug from enzymatic and acidic degradation. It shows

excellent entrapment efficiency and in vitro drug release. Niosomes have a very important and key role in various types of drug deliveries; like targeting, topical, oral, ophthalmic, and parenteral. There is a lot of scope to encapsulate toxic drugs involved in different type of drug classification. Niosomes are very useful in bright future for pharma industries and drug discovering areas.

## ACKNOWLEDGMENT

I am grateful to Mrs. Sheri P. S. (Associate Professor in Pharmaceutics) for providing the guidance and support for publishing this article. I am highly tanksful to my colleagues Ms. Anu Mathew and Ms. Susan Jacob for the continuous encouragement and assistance for completing the article.

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